Remarks:

Information Disclosure Statement

In paragraph 2, the Office Action refers to FR 2577410. The Office Action also includes a copy of a PTO-1449 form which appears to be related to U.S. Application Serial No. 10/634,664, entitled "Light Delivery Catheter," and appears unrelated to the instant application. Accordingly, Applicants believe that the discussion of FR 2577410 and the inclusion of the PTO-1449 from 10/634,664 was erroneous.

Claim Rejections - 35 U.S.C. §103(a)- Cicco (US 5,026,924)

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cicco ("the '924 patent"). In particular, the Office Action asserts that although the '924 patent does not specifically disclose the claimed amounts of antimony pentachloride and hydrogen fluoride, it clearly suggests them. The Office Action purports that differences in concentration and temperature in the claimed method will not support patentability of the claimed method due to the absence of a showing that such concentration and temperature are critical. Furthermore, the Office Action posits that the difference in the additional reaction time (after the addition of hydrogen fluoride) is obvious to one of ordinary skill in the art.

The Examiner notes that the comparative data provided in the Example section was considered, but is not deemed unexpected in view of the teachings of the '924 patent. The Office Action contends that one of skill in the art would conclude that by varying the ratio of isoflurane to hydrogen fluoride the yield of desflurane and conversion of isoflurane could be altered. Moreover, the Office Action asserts that the data provided in the specification fails to overcome a prima facie obviousness rejection because the comparison provided in the specification is not a side-by-side comparison. The Examiner reasons that the comparison presented is between the instant invention and Example 1 of the '924 patent, rather than a comparison between the amount of antimony pentachloride and hydrogen fluoride present in Example 1 with the claimed amounts of antimony pentachloride and hydrogen fluoride under identical reaction conditions.

Applicants respectfully disagree. First, in contrast to merely varying the yield of desflurane and conversion of isoflurane, Applicants' invention relates to a method that results in significantly lower levels of by-products in the crude reaction product (see the discussion of the

result obtained in Example 5 *infra*). Due to the lower levels of by-products, the isolation of purified desflurane from the crude reaction product is considerably less complex than the isolation of desflurane crude products containing higher levels of by-products.

In particular, as noted in paragraph 4 of the specification, the reaction of isoflurane and hydrogen fluoride provides desflurane according to the equation (1):

$$CF_3CHClOCHF_2 + HF + SbCl_5 \text{ (cat.)} \rightarrow CF_3CHFOCHF_2 + HCl \quad (1)$$

In addition to forming desflurane, a major proportion of the by-products formed is bis-1,2,2,2-tetrafluoroethyl ether ($CF_3CHFOCHFCF_3$). Formation of this by-product and other structurally related by-products increases the complexity of the subsequent purification of desflurane. Multiple distillation stages are typically needed to separate the two stereoisomers of bis-1,2,2,2-tetrafluoroethyl ether impurity from useful materials. Moreover, distillation fractions containing the by-products often contain substantial quantities (e.g., >99 percent by weight) of desflurane. Due to the fact that additional separations of the contaminated fractions are unfavorable from the standpoint of economics, these fractions are typically discarded, lowering the isolated yield of the purified desflurane product. Accordingly, it is advantageous to adjust the reaction conditions for reaction (1) to minimize the levels of by-products present in the crude reaction product, as is provided by the claimed invention.

Second, a side-by-side comparison of the results obtained for two sets of experimental trials conducted *under identical reaction conditions* is presented in the instant specification (see Table 4 of Example 5, paragraphs 54 through 55). Row 1 of Table 4 shows the results of conducting trials using quantities of hydrogen fluoride and antimony pentachloride that are within the scope of the claimed method. Row 2 of Table 4 shows the results of conducting trials using quantities of hydrogen fluoride and antimony pentachloride consistent with Example 1 of the '924 patent (i.e, "reference conditions"). The two sets of trials differ only in the molar ratios of isoflurane/HF and in the mole% of antimony pentachloride. Other reaction parameters were identical. The comparison in Table 4 readily allows the skilled artisan to conclude that the claimed concentrations of antimony pentachloride and hydrogen fluoride provide unexpected results in terms of reduced levels of by-products in the crude reaction product. As exhibited in Table 4, while the concentration of desflurane in the crude reaction product obtained under both sets of trials are similar (i.e., 93.43% vs. 96.55%), the level of by-product (i.e., 0.47%) obtained

using the claimed ratio of reagents is 3 fold less than that obtained under the reference conditions (i.e., 1.41%).

The reaction conditions under which both sets of trials were conducted for the comparison are described in paragraphs 39 through 41 (Example 1) of the instant specification. In addition, the analytical method (GC) is further described in paragraph 41.* In brief, while the quantities of antimony pentachloride and hydrogen fluoride are different between the two sets of conditions in Table 4; the reaction time, temperature, rate of HF addition and reaction workup were identical.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

* Example 2 of the instant specification (paragraph 41 through 45) further describes the "reference set of conditions" which mimic the conditions described in Example 1 of the '924 patent. As noted in Example 2 of the instant specification, the quantities of reagents used to conduct the reaction were scaled down from a pilot plant scale described in the '924 patent (e.g., isoflurane = 166.4 kg) to a more convenient scale (e.g., isoflurane = 154.0 g) to facilitate the comparison. The molar ratio of isoflurane and hydrogen fluoride and the mole% of antimony pentachloride used in the scaled down reference set of conditions is identical with that used in Example 1 of the '924 patent.

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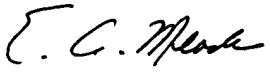
Closing Remarks

Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration in view of this response and allowance of the pending claims are earnestly solicited.

Respectfully submitted,



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